Serial No. 10/640,853
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-10998.01	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/25368	International filing date *(day/month/year)* 13.08.2003	Priority date *(day/month/year)* 13.08.2002
International Patent Classification (IPC) or both national classification and IPC A61L27/54		
Applicant MEDTRONIC, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.03.2004	04.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Epskamp, S Telephone No. +31 70 340-2857

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/25368

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29, 33, 34, 37-62	as originally filed
30-32, 35, 36	received on 18.03.2004 with letter of 12.03.2004

Claims, Numbers

1-57, 63(part), 64-74	as originally filed
58-62, 63(part)	received on 18.03.2004 with letter of 12.03.2004

Drawings, Sheets

1/23-23/23	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-74 (part)

   because:

   ☒ the said international application, or the said claims Nos. 71-74 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-74 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-74
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-74
Industrial applicability (IA)	Yes:	Claims	1-70
	No:	Claims	

2. Citations and explanations

see separate sheet

ITEM III

Claims 71-74 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

No opinion will be given as to novelty, inventive step and industrial applicability of the subject-matter for which no International Search Report was established (Rule 66.1(e) PCT).

ITEM V

The following documents are referred to:

D1: EP 0 347 145 A

D2: WO 93/00058 A

D3: Apicella A et al. (1993) Biomaterials 14: 83-90

D4: WO 01/78626 A

No opinion will be given as to novelty, inventive step and industrial applicability of the subject-matter for which no International Search Report was established (Rule 66.1(e) PCT).

I - Clarity, Disclosure

Independent claims 1, 10, 20, 32, 56 and 63 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define, by the use of a multitude of parameters, the subject-matter in terms of the result to be achieved. In this instance such a formulation is not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved (PCT International Search and Examination Guidelines 5.35).

Furthermore, the following parameters from the independent claims do not fulfill the criteria outlined in Guidelines 5.36, in that they, as claimed, **cannot** be clearly and reliably determined:

- "Solubility parameter": As is known to the person skilled in the art, different methods of measuring and/or calculating solubility parameters lead to significantly different results. This is also reflected in the description of the application (see page 19, lines 6-21; page 24, notes and page 26, lines 10-13).

For instance, while according to Table 1 the solubility parameter of dexamethasone is 27.25 $J^{1/2}/cm^{3/2}$ (the "average of the calculated values based on Hofteyzer and Van

Krevelen's [...] method [...] and Hoy's method", see note 2 on page 24), on page 26 two other values for the solubility parameter of dexamethasone are given, 27 $J^{1/2}/cm^{3/2}$ ("Group Contribution Methods") and 21 $J^{1/2}/cm^{3/2}$ ("Molecular Dynamics Methods").
As the different methods to measure or calculate "the" solubility parameter result in different values for this parameter, in the absence of any unambiguous indication in the claims which method for determining this parameter is to be used, the subject-matter of independent claims 1, 10, 20, 32, 56 and 63 is considered to lack clarity (Article 6 PCT).
As the description appears to be silent about which method is actually used or even preferred in view of the definitions used in the claims, the application as a whole would also appear to lack disclosure (Article 5 PCT).
- "Diffusivity": It would be expected that the diffusivity of a polymer for an active agent is dependent on environmental conditions, e.g. the temperature. In the absence of an indication of the measuring conditions for this parameter in the claims, the subject-matter of claims 1, 10, 20, 32, 56 and 63 is considered to lack clarity (Article 6 PCT). Again, as the application is silent about the measuring conditions for this parameter, the application is also considered to lack disclosure (Article 5 PCT).
- "Swellability": Again, it would be expected that the swellability of a polymer blend depends e.g. on the medium (water according to the description?), the environmental temperature, pressure etc. As these conditions are not defined in the claims nor in the description, the subject-matter of claims 1, 10, 20, 32 lacks clarity (Article 6 PCT) and the application as a whole lacks disclosure (Article 5 PCT).

In addition, the terms "hydrophobic" (claims 1, 20) and "hydrophilic" (claims 10, 32) are relative terms which do not have a generally accepted meaning which would allow the skilled person to unambiguously determine whether a compound is hydrophobic or hydrophilic (Guidelines 5.34). As a consequence a further lack of clarity is seen for claims 1, 10, 20 and 32 (Article 6 PCT)..

Independent claims 1 and 20, and claims 10 and 32, respectively, appear to be identical, leading to a (further) lack of clarity and conciseness (Article 6 PCT).

II - Novelty and Inventive Step

In view of the above, no full analysis of novelty and inventive step (Article 33(2) and (3) PCT) can be given (see also Item III: Rule 66.1(e) PCT).
It would however appear, that similar if not identical concepts, i.e. drug delivery devices comprising an active agent dispersed in a matrix of two polymers, wherein active agent release can be regulated by the nature and the proportions of the polymers, are disclosed in the following documents:

D1 (page 2, line 43 - page 3, line 39; page 4, line 31 - page 5, line 11; page 6, line 40 - page 7, line 9; examples; claims),
D2 (page 5, lines 3-8; page 5, line 24 - page 6, line 14; page 16, lines 3-25; examples, notably examples 3 and 4; claims),
D3 (abstract; page 84, left-hand column, 2nd par.),
D4 (page 5, lines 1-20; page 10, line 33 - page 11, line 6; examples; claims).

As a consequence, at present the subject-matter of claims 1-74 is considered to lack novelty and inventive step (Article 33(2) and (3) PCT).

III - Industrial applicability

The subject-matter of claims 1-70 is considered to fulfill the requirements of Article 33(4) PCT (see also Item III).

than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is no greater than 10% by volume.

Examples of suitable combinations of polymer blends for the first group of active agents are described in greater detail in Applicants' Assignee's copending applications entitled: ACTIVE AGENT DELIVERY SYSTEM INCLUDING A HYDROPHOBIC CELLULOSE DERIVATIVE, MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,477, filed on August 13, 2002, and U.S. Patent Application Serial No. 10/640,714, filed on even date herewith; ACTIVE AGENT DELIVERY SYSTEM INCLUDING A POLYURETHANE, MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,478, filed on August 13, 2002, and U.S. Patent Application Serial No. 10/640,823, filed on even date herewith; and ACTIVE AGENT DELIVERY SYSTEM INCLUDING A POLY(ETHYLENE-CO-(METH)ACRYLATE), MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,413, filed on August 13, 2002, and U.S. Patent Application Serial No. 10/640,702, filed on even date herewith. Specific examples of such blends are illustrated in the Examples Section. Preferably, the miscible polymer blend suitable for use with the first group of active agents does not include the following: a blend of a hydrophobic cellulose derivative and a polyurethane or polyvinyl pyrrolidone; and/or a blend of a polyalkyl methacrylate and a polyethylene-co-vinyl acetate.

For a second group of active agents that are hydrophilic and have a molecular weight of no greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the molar average solubility parameter of the blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is no greater than 10% by volume.

Examples of suitable polymers for systems that deliver an active agent from this second group include polyacrylonitriles, cyanoacrylates, methacrylonitriles, hydrophilic cellulosics, and the like, and combinations

thereof. In this context, "combination" means mixtures and copolymers thereof. The mixtures and copolymers can include one or more members of the group and/or other monomers/polymers. Preferably, the miscible polymer blend suitable for use with the second group of active agents does not include both a hydrophobic cellulose derivative and a polyvinyl pyrrolidone.

Examples of suitable combinations of polymer blends for the first group of active agents are described in greater detail in Applicants' Assignee's copending application entitled ACTIVE AGENT DELIVERY SYSTEM INCLUDING A POLYURETHANE, MEDICAL DEVICE, AND METHOD, having U.S. Patent Application Serial No. 10/640,823, filed on even date herewith.

For a third group of active agents that are hydrophobic and have a molecular weight of greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the molar average solubility parameter of the blend is no greater than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is greater than 10% by volume.

Examples of suitable polymers for systems that deliver an active agent from this third group include at least one hydrophobic polymer including hydrophobic cellulose derivatives such as methyl cellulose, ethyl cellulose, hydroxy propyl cellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose nitrate, hydroxypropyl methyl cellulose, hydroxypropyl ethyl cellulose, methyl ethyl cellulose, cellulose acetate propionate, cellulose acetate butyrate, cellulose propionate butyrate, cellulose acetate propionate butyrate, and combinations thereof. The polymer blends for these systems can include a second polymer that is either hydrophobic or hydrophilic. For example, the hydrophilic polymer can be a hydrophilic polyurethane. A preferred hydrophilic polyurethane includes soft segments having therein polyethylene oxide units. Examples of suitable hydrophilic polyurethanes are poly(ether urethanes) available from Thermedics, Inc. (Woburn, MA), under the tradename TECOPHILIC. Preferably, the miscible polymer blend suitable for use with the third group of active agents does not

include the following: a blend of a hydrophobic cellulose derivative and a polyurethane or polyvinyl pyrrolidone; and/or a blend of a polyalkyl methacrylate and a polyethylene-co-vinyl acetate.

For a fourth group of active agents that are hydrophilic and have a molecular weight of greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the molar average solubility parameter of the blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is greater than 10% by volume.

Examples of suitable combinations of polymer blends for the fourth group of active agents are described in greater detail in Applicants' Assignee's copending applications entitled ACTIVE AGENT DELIVERY SYSTEM INCLUDING A HYDROPHILIC POLYMER, MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,392, filed on August 13, 2002, and U.S. Patent Application Serial No. 10/640,713, filed on even date herewith. Specific examples of such blends are illustrated in the Examples Section. Preferably, the miscible polymer blend suitable for use with the fourth group of active agents does not include both a hydrophobic cellulose derivative and a polyvinyl pyrrolidone.

The polymers in the miscible polymer blends can be crosslinked or not. Similarly, the blended polymers can be crosslinked or not. Such crosslinking can be carried out by one of skill in the art after blending using standard techniques.

In the active agent systems of the present invention, the active agent passes through a miscible polymer blend having a "critical" dimension. This critical dimension is along the net diffusion path of the active agent and is preferably no greater than about 1000 micrometers (i.e., microns), although for shaped objects it can be up to about 10,000 microns.

preferred metal is stainless steel, a nickel titanium alloy, such as NITINOL, or a cobalt chrome alloy, such as NP35N.

A polymeric coating that includes a miscible polymer blend can adhere to a substrate surface by either covalent or non-covalent interactions. Non-covalent interactions include ionic interactions, hydrogen bonding, dipole interactions, hydrophobic interactions and van der Waals interactions, for example.

Preferably, the substrate surface is not activated or functionalized prior to application of the miscible polymer blend coating, although in some embodiments pretreatment of the substrate surface may be desirable to promote adhesion. For example, a polymeric undercoat layer (i.e., primer) can be used to enhance adhesion of the polymeric coating to the substrate surface. Suitable polymeric undercoat layers are disclosed in Applicants' Assignee's copending U.S. Provisional Application Serial No. 60/403,479, filed on August 13, 2002, and U.S. Patent Application Serial No. 10/640,701, filed on even date herewith, both entitled MEDICAL DEVICE EXHIBITING IMPROVED ADHESION BETWEEN POLYMERIC COATING AND SUBSTRATE. A particularly preferred undercoat layer disclosed therein consists essentially of a polyurethane. Such a preferred undercoat layer includes a polymer blend that contains polymers other than polyurethane but only in amounts so small that they do not appreciably affect the durometer, durability, adhesive properties, structural integrity and elasticity of the undercoat layer compared to an undercoat layer that is exclusively polyurethane.

When a stent or other vascular prosthesis is implanted into a subject, restenosis is often observed during the period beginning shortly after injury to about four to six months later. Thus, for embodiments of the invention that include stents, the generalized dissolution rates contemplated are such that the active agent should ideally start to be released immediately after the prosthesis is secured to the lumen wall to lessen cell proliferation. The active agent should then continue to dissolute for up to about four to six months in total.

The invention is not limited by the process used to apply the polymer blends to a substrate surface to form a coating. Examples of suitable coating processes include solution processes, powder coating, melt extrusion, or vapor deposition.

A preferred method is solution coating. For solution coating processes, examples of solution processes include spray coating, dip coating, and spin coating. Typical solvents for use in a solution process include tetrahydrofuran (THF), methanol, ethanol, ethylacetate, dimethylformamide (DMF), dimethyacetamide (DMA), dimethylsulfoxide (DMSO), dioxane, N-methyl pyrollidone, chloroform, hexane, heptane, cyclohexane, toluene, formic acid, acetic acid, and/or dichloromethane. Single coats or multiple thin coats can be applied.

Similarly, the invention is not limited by the process used to form the miscible polymer blends into shaped objects. Such methods would depend on the type of shaped object. Examples of suitable processes include extrusion, molding, micromachining, emulsion polymerization methods, electrospray methods, etc.

For preferred embodiments in which the active agent delivery system includes one or more coating layers applied to a substrate surface, a preferred embodiment includes the use of a primer, which is preferably applied using a "reflow method," which is described in Applicants' Assignee's copending U.S. Provisional Application Serial No. 60/403,479, filed on August 13, 2002, and U.S. Patent Application Serial No. 10/640,701, filed on even date herewith, both entitled MEDICAL DEVICE EXHIBITING IMPROVED ADHESION BETWEEN POLYMERIC COATING AND SUBSTRATE.

Preferably, in this "reflow method," the device fabrication process involves first applying an undercoat polymer to a substrate surface to form the polymeric undercoat layer, followed by treating the polymeric undercoat layer to reflow the undercoat polymer, followed by applying a miscible polymer blend, preferably with an active agent incorporated therein, to the reformed undercoat layer to form a polymeric top coat layer. Reflow of the undercoat polymer can be accomplished in any

58. The method of claim 56 wherein miscible polymer blend initially provides a barrier for permeation of the active agent.

59. The method of claim 56 wherein the active agent is incorporated within an inner matrix.

60. The method of claim 56 wherein the active agent is hydrophobic.

61. The method of claim 56 wherein the active agent is hydrophilic.

62. The method of claim 48 wherein:

the miscible polymer blend does not include a blend of a hydrophobic cellulose derivative and a polyurethane or a polyvinyl pyrrolidone; and/or

the miscible polymer blend does not include a blend of a polyalkyl methacrylate and a polyethylene-co-vinyl acetate.

63. A method of designing an active agent delivery system for delivering an active agent over a preselected dissolution time (t) through a preselected critical dimension (x) of a miscible polymer blend, the method comprising:

providing an active agent having a molecular weight greater than about 1200 g/mol;

selecting at least two polymers, wherein:

the difference between the solubility parameter of the active agent and at least one solubility parameter of each of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of the at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; and

the difference between the swellabilities of the at least two polymers is sufficient to include the target diffusivity;

combining the at least two polymers to form a miscible polymer blend;